Recanalization Rates after Endovascular Coil Embolization in a Cohort of Matched Ruptured and Unruptured Cerebral Aneurysms

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Summary

The aim of this study was to retrospectively assess the recanalization rate, factors associated with and time taken for recanalization to occur in a matched ruptured and unruptured aneurysm population that were treated with endovascular coiling.

Ruptured and unruptured aneurysms treated between 2002 and 2007 were matched for aneurysm location, diameter and neck size. Recanalization rate, time to recanalize, re-treatment rate and clinical outcome were analysed.

Ninety-eight matched ruptured and unruptured aneurysms (49 aneurysms in each group) were studied. 46.8% of aneurysms in the ruptured group achieved complete obliteration on the initial post treatment angiogram versus 34.7% in the unruptured group. The ruptured group had a higher rate of recanalization (40.4% versus 20.4%). 25.5% of aneurysms had significant recanalization in the ruptured group versus 6.1% in the unruptured group (p=0.009). The retreatment rate was higher in the ruptured group (21.3% versus 6%). Ruptured aneurysms took a shorter time to recanalize with a mean time of 5.3±3.8 months versus 12.4±7.7months (p=0.003). Multivariate logistic regression analysis found neck size (p=0.0098), wide neck morphology (p=0.0174), aneurysm diameter (p< 0.0001) and ruptured aneurysms (p=0.0372) were significant predictors of recanalization. The majority of patients in both groups had a good outcome with GOS=5 (85.7% and 83.7%) but two deaths occurred in the ruptured group.

Ruptured and unruptured aneurysms showed significant differences in rate, degree and timing of recanalization, thus requiring different protocols for imaging follow-up post endovascular treatment. Earlier and more frequent imaging follow-up is recommended for ruptured aneurysms.

Introduction

Endovascular coil embolization is a well-established treatment for cerebral aneurysms since its introduction almost two decades ago [1-6]. Recanalization is still a significant occurrence when compared to surgical clipping [7,8]. Recanalization, if significant, often requires retreatment either by re-coiling or surgical clipping. Factors related to an increased risk of recanalization have been studied but only in the context of an entire aneurysm population with combination of ruptured and unruptured aneurysms in an unmatched population [8]. The aim of this study was to retrospectively assess the rate of recanalization, factors associated with recanalization and time taken for recanalization to occur in a matched population of ruptured and unruptured aneurysms treated endovascularly. The aneurysms were matched for location, aneurysm diameter and size. All aneurysms were treated by a group of experienced interventional neuroradiologists in a single centre and follow-up was over a similar time period. Our goal was to identify a subpopulation of aneurysms at higher risk of recanalization. Such knowledge may assist in patient selection for coiling. The timing of recanalization may be useful in planning follow-up imaging.

Methodology

Patient population

A review of the intracranial aneurysm database maintained at Toronto Western Hospital was performed. Only patients treated from 2002 to 2007 were reviewed. All patients with unruptured aneurysms treated with endovascular technique were first reviewed and they were matched for aneurysm size, location and neck size to the ruptured aneurysms also treated by endosaccular coiling. Where possible, sex and age were also matched. Clinical presentation, imaging and outcome were reviewed with the main focus being recanalization rate, time taken for recanalization, re-treatment rate and clinical outcome. Aneurysms treated with vessel occlusions were excluded from the study. This study was approved by the institutional review board, and individual patient consent was obtained.

Endovascular technique

Coil embolization for ruptured aneurysms was performed as soon as possible following subarachnoid haemorrhage and was based on the review of the admission CTA to ensure that the morphology of the aneurysm was suitable for coil embolization. In the setting of multiple aneurysms, the aneurysm thought to be the most likely cause of subarachnoid haemorrhage was treated first. If clinically suitable, coiling of multiple aneurysms was performed in a single setting if the morphology of the aneurysms was deemed suitable to be treated via coil embolization. Unruptured aneurysms were treated after discussion with the patient in the outpatient clinic and following the recommendation of our multidisciplinary conference held by interventional neuroradiologists and neurosurgeons and following review of CT angiography with or without digital subtraction angiography (DSA).

Endovascular coiling technique

All endovascular treatments were performed under general anaesthesia with systemic anticoagulation via heparin administration. The activated clotting time (ACT) was kept between 250 and 300 seconds. Platinum coils were the main coils used in both study populations. The coils used were Guglielmi detachable coils (GDC; Boston Scientific, Natick, MA, USA), MicroCoils (Micrus; San Jose, CA, USA), MicroPlex coils (Microvention; Aliso Viejo, CA, USA), and Trufill DCS coils (Cordis; Miami Lakes, FL, USA). Matrix coils (Boston Scientific) and Hydrocoils (Microvention) were also used in a small percentage of cases. In the unruptured population, three cases were treated predominantly by Hydrocoil compared to a single case in the ruptured population. Matrix coils were the predominant coils used in two cases in the unruptured population compared to no predominant usage of Matrix coils in the ruptured population.

Balloon or stent-assisted techniques were used in aneurysms with wide-neck morphology. The balloon-assisted technique was the preferred option. The aim of coil placement was to pack the aneurysm as densely as possible with the hope to achieve complete occlusion.

Follow-up

Prior to 2005, cases were followed up using digital subtraction angiography (DSA) with 3D rotational angiography. From 2005, cases were followed using MR angiography (MRA) using the "autotriggered elliptical centric-ordered" (ATECO) 3D gadolinium-enhanced technique [9,10]. Follow-up imaging was always compared to the initial post-embolization DSA. Two types of follow-up protocols were used over the study period. Prior to 2005, imaging studies were performed prior to discharge, at six months, and at 18 months after treatment. After 18 months, those with completely occluded aneurysms were imaged once every two years, and those with remnants were followed up once a year. After 2005, the protocol was altered to include an additional imaging study at two to three months after treatment. Clinical evaluations were performed in our outpatient brain aneurysm clinic which is attended by interventional neuroradiologists and cerebrovascular surgeons. These were carried out at two and six months post treatment and followed by yearly visits.

Evaluation of angiographic results

Pre-treatment maximum aneurysm diameter and neck sizes were measured on digital subtraction angiography and/or computed tomographic angiogram (CTA). In the literature, aneurysms have been classified as having a "wide" neck with dome-to-neck ratio of less than 1.5 or 2 [11-13]. We used a dome- to- neck ratio of < 1.8 to classify the aneurysm as "wide" neck, and a ratio of ≥ 1.8 as for "narrow" neck morphology. The aspect ratio was measured (height to neck ratio) [14]. The morphology of pre-treatment aneurysm was classified as smooth dome or irregular. Bilobed aneurysms, aneurysms with daughter blebs and multilobulated morphology were all classified as irregular.

The initial aneurysm obliteration was classified as i) complete, ii) residual neck or iii) residual body [15]. Follow-up aneurysm assessment was classified as i) further thrombosis ii) stable iii) mild recanalization or iv) significant recanalization. An aneurysm was classified as "further thrombosis" if further obliteration of aneurysm on follow-up imaging was found in comparison to the initial obliteration state. The aneurysm was considered "stable" if there was no change compared to the initial post embolization angiogram. Recanalization was "mild" if there was an increase in the contrast opacification within the neck that was greater than the initial obliteration. Recanalization was "significant" if there was an increase in the contrast opacification of the aneurysm body which was greater than the initial and re-treatment was considered [8,16].

Time taken for recanalization was measured as the time between the embolization and the first time recanalization was noted on follow-up imaging.

Statistical analysis

Statistical analysis was performed using SAS System v.9.1.3 (SA Institute, Cary, NC, USA). Univariate and multivariate statistical analysis was performed, adjusting for sex, age, aneurysm diameter size, aneurysm neck size, aneurysm neck morphology, aneurysm morphology, Aspect ratio, location and initial aneurysm obliteration to assess significant factors related to recanalization.

Results

Forty-nine aneurysms were matched for aneurysm diameter, location and neck size from the unruptured group to the ruptured group. There were a total of 47 patients in the unruptured group (with two patients contributing two aneurysms) and 48 patients in the ruptured group (with one patient contributing two aneurysms). The unruptured group had 78.7% females and the ruptured group had 81.3%. The mean age for the unruptured versus the ruptured group is 51±10 yrs versus 49±14 yrs with a mean follow up of 20.6±15.2 months versus 25.1±19.5 months (Table 1). 87.8% of the ruptured group and 55.1% of the unruptured group were treated with coiling alone. A higher percentage (28.6% versus 12.2%) of patients in the unruptured group required balloon remodelling technique. 16.3% of patients from the unruptured group required stent assistance while none of the patients in the ruptured group required stent assistance. 75.5% of the treated aneurysms were located in the anterior circulation (Table 2).

Clinical outcome

Good outcome with GOS=5 was achieved in 91.5% of the unruptured group versus 85.4% in the ruptured group. Two patients from the ruptured aneurysm group died (GOS=1) due to severe vasospasm and large infarcts. Two patients had GOS=3 and three patients had GOS=4 in the ruptured group. Of the patients with GOS= 4, one patient had multiple embolic infarcts post embolization and two patients had moderate to severe vasospasm, one leading to a large MCA infarct. Four patients in the unruptured group had GOS=4, all not related to periprocedural complications. Of those four patients, three had chronic major vascular territory infarcts contributing to the pre-treatment morbidity.

Procedural complications

Periprocedural complications are listed in Table 3. A single patient had two periprocedural complications, aneurysm perforation and adjacent vessel occlusion. The complications were recorded separately. None of the periprocedural complications led to permanent morbidity or mortality in either group. The patient with an aneurysm perforation in the ruptured group had a transient third nerve palsy. Two patients with aneurysm perforation in the unruptured group were treated promptly with reversal of heparin with protamine and balloon inflation. Neither patient had transient or permanent morbidity. Parent vessel occlusions and clot in stent were treated promptly with Abciximab (ReoPro; Eli Lilly, Indianapolis, IN, USA) with

Table 1 **Patient background, treatment and follow-up characteristics.**

	Unruptured aneurysm, (n=49)	**Ruptured aneurysm (n=49)**
Sex, female, n (%)	37/47 (78.7)	39/48 (81.3)
Age (mean ±SD) yrs	51±10	49±14
Mean follow-up time (mths)±SD	20.6±15.2	25.1±19.5
Treatment: Coil only, no. (%)	27/49 (55.1)	43/49 (87.8)
Coil & Balloon	14/49 (28.6)	6/49 (12.2)
Coil & Stent	8/49 (16.3)	0/49 (0)
Re-haemorrhage, no.	0/49	0/49
Outcome (Glasgow outcome score):		
1	0	2
2	0	0
3	0	2
4	4	3
5	43/47(91.5%)	41/48(85.4%)

no associated infarct or neurological deficit. The patient in the ruptured group with iatrogenic right ICA dissection did not progress to infarct and the vessel remained patent post procedure. No re-hemorrhage occurred in the ruptured group. There were no haemorrhages in the follow-up in the unruptured group.

Aneurysm characteristics

There was no significant difference in the mean diameter of the unruptured aneurysm group (8.3±2.8 mm) versus ruptured aneurysm group (8.3±3 mm) with a mean aneurysm neck diameter of 4.1±1.4 mm vs 3.9±1.3 mm (Table 4). The unruptured group had a higher number of patients with wide neck morphology. The aneurysm dome morphology was smooth in majority of patients in the unruptured group (67.3%) and irregular in the ruptured group (61.2%).

Table 2 **Aneurysm location*** **number (%)**

Anterior circulation	**37 (75.5)**
Anterior communicating artery	7 (14.3)
Posterior communicating artery	9 (18.4)
Paraophthalmic artery	10 (20.4)
Middle cerebral artery	3 (6.1)
Anterior choroidal artery	1 (2.0)
Internal carotid artery termination	7 (14.2)
Posterior circulation	**12 (24.5)**
Basilar artery	9 (18.4)
Posterior inferior cerebellar artery	2 (4.1)
Vertebral artery	1 (2.0)

**matched aneurysm location for ruptured and unruptured aneurysms.*

Coiling results

Complete obliteration of the aneurysm in the initial post treatment state was achieved more commonly in the ruptured group compared to the unruptured group with 46.8% versus 34.7% (Table 5). After treatment, there were residual neck remnants in the majority of patients in both groups (55.1% for the unruptured group and 51.1% for the ruptured group). Five patients (10.2%) in the unruptured group had body remnants versus one patient (2.1%) in the ruptured group.

Imaging follow-up

Despite having a lower number of aneurysms with complete obliteration and higher percentage of residual body remnants and wide neck morphology, the unruptured aneurysm group has a lower rate of recanalization (20.4%) compared to the ruptured aneurysm group (40.4%) (p=0.03) (Table 6). 25.5% of aneurysms in the ruptured aneurysm group had significant recanalization versus 6.1% in the unruptured group

Table 3 **Periprocedural Complications.**

	Unruptured, n (%)	Ruptured, n (%)
Aneurysm perforation	2 (4)	1 (2)
Parent vessel occlusion	1 (2)	1 (2)
Clot in stent	1 (2)	0 (0)
Arterial dissection	0 (0)	1 (2)
Distal emboli	2 (4)	3 (6)

Table 4 **Pre-treatment aneurysm characteristics.**

	Unruptured aneurysm	Ruptured aneurysm	P-value
Diameter, mm (mean±SD)	8.3±2.8	8.3±3.0	0.95 (NS)
Neck size, mm (mean±SD)	4.1±1.4	3.9±1.3	0.65 (NS)
Neck morphology (wide), no. (%)	26 (53.1)	20 (40.8)	0.22 (NS)
Aspect ratio (mean±SD)	2.1±0.7	1.9±0.6	0.21 (NS)
Aneurysm morphology, no.(%)			**0.006**
Smooth	33 (67.3)	19 (38.8)	
Irregular	16 (32.7)	30 (61.2)	

Table 5 **Initial post treatment obliteration (p=0.08).**

	Unruptured aneurysm(n=49)	Ruptured aneurysm(n=47)
Complete, no. (%)	17/49 (34.7)	22/47 (46.8)
Residual neck, no. (%)	27/49 (55.1)	24/47 (51.1)
Residual body, no. (%)	5/49 (10.2)	1/47 (2.1)

Table 6 **Follow-up aneurysm obliteration and recanalization, no. (%).**

	Unruptured aneurysm (n=49)	Ruptured aneurysm (n=47)	P=value
Further thrombosis	15/49 (30.6)	1/47 (2.1)	**0.0001**
Stable	24/49 (49)	27/47 (57.4)	0.41
Recanalization	**10/49 (20.4)**	**19/47 (40.4)**	**0.03**
Mild	7/49 (14.3)	7/47 (14.9)	0.86
Significant	3/49(6.1)	12/47 (25.5)	**0.009**
Time taken to recanalization, mths (mean±SD)	12.4±7.7	5.3±3.8	**0.003**

(p=0.009). 30.6% of aneurysms in the unruptured aneurysm group went on to further thrombosis when compared to 2.1% in the ruptured group (p=0.0001).

Of the five aneurysms in the unruptured group that had a body remnant, two went on to complete occlusion and three further thrombosed to a tiny neck of 1-2 mm. The only aneurysm with body remnant in the ruptured group went on to have significant recanalization at the three month follow-up.

Recanalization and re-treatment

The ruptured aneurysm group took a significantly much shorter time to recanalize with a mean time of 5.3±3.8 months versus 12.4±7.7 months for the unruptured group (p=0.003). Ten aneurysms in the ruptured group required re-treatment. Three patients had recoiling, three patients had recoiling with stent assistance, one patient had recoiling with balloon assistance and three patients underwent surgical clipping. Within the unruptured group, two aneurysms had recoiling only and one had surgical clipping. The retreatment rate was 21.3% in the ruptured group versus 6% in the unruptured group.

Univariate logistic regression analysis was performed after dichotomizing patient population into recanalized and non-recanalized groups (Table 7). The recanalized group tend to be ruptured (p=0.05), have larger aneurysm diameter (p=0.005), wide neck morphology (p=0.02) and larger size neck (p=0.05). The recanalized group had a higher percentage of aneurysms located in the posterior circulation compared to the non-recanalized group (27.9% versus 19.4%, p=0.05). Incomplete obliteration after initial treatment was more prevalent in the recanalized group versus non-recanalized group (79.3% versus 65.7%), although this was not statistically significant (p=0.4).

Multivariate logistic regression analysis, after adjusting for confounders, showed that neck size (p=0.0098), wide neck morphology (p= 0.0174), aneurysm diameter (p<0.0001) and ruptured aneurysms (p=0.0372) were significant predictors for recanalization (Table 8).

Table 7 **Univariate logistic regression analysis for recanalization.**

	Recanalized (n=29)	Non-recanalized (n=67)	p-value
Ruptured vs unruptured, no. (%)	19/29 (65.5) vs 10/29 (34.5)	28/67(41.8) vs 39/67 (58.2)	**0.05**
Age, yrs (mean±SD)	53.9±14.7	50.9±10.8	0.26
Neck size, mm (mean±SD)	4.4±1.3	3.8±1.4	**0.05**
Neck morphology, wide vs narrow, no. (%)	19/29 (65.5) vs 10/19 (34.5)	27/67 (40.3) vs 40/67 (59.7)	**0.02**
Aneurysm diameter, mm (mean±SD)	9.6±2.6	7.8± 2.9	**0.005**
Aspect ratio	2.1±0.7	2.0±0.6	0.57
Dome morphology: smooth vs complex, no. (%)	14/29 (48.2) vs 15/29 (51.8)	38/67 (56.7) vs 29 (43.3)	0.54
Circulation: Anterior vs posterior, no. (%)	18/29 (62.1) vs 11/29 (27.9)	54/67 (80.6) vs 13/67 (19.4)	**0.05**
Initial obliteration state: complete vs incomplete, no. (%)	6/29 (20.7) vs 23/29 (79.3)	23/67 (34.3) vs 44/67 (65.7)	0.41

Table 8 **Multivariate logistic regression analysis for recanalization, controlling for confounders.**

Predictor	Statistical significance	Odds ratio (95% CI)
Neck size	**p=0.0098**	**0.47 (0.27-0.84)**
Wide vs narrow neck morphology	**p=0.0174**	**7.93 (1.44- 43.70)**
Aneurysm diameter	**p<0.0001**	**1.70 (1.31-2.22)**
Age	p=0.0572	1.40 (1.00-1.08)
Ruptured vs unruptured	**p=0.0372**	**6.22 (1.11-34.73)**
Posterior vs Anterior location	p=0.9611	1.02 (0.39-2.72)
Aneurysm morphology (complex vs smooth)	p=0.5217	0.64(0.17-2.47)
Aspect's ratio	p=0.4961	0.69 (0.23-2.03)

Discussion

Our study confirms that the risk of recanalization, for matched populations of ruptured and unruptured cerebral aneurysms treated with endovascular coil embolization, is significantly higher in the ruptured group. This finding is consistent with those found in other studies [8,16,17]. Nguyen et al. found a recanalization rate of 53.5% in the ruptured aneurysms versus 22.5% for unruptured aneurysms (p=0.001) [8]. Not only was there an increased risk of recanalization, but the vast majority of the recanalizations that occurred in the ruptured group were significant, requiring re-treatment by either re-coiling (with or without stent/balloon assistance) or surgical clipping. A significantly shorter time for recanalization occurred in ruptured aneurysms when compared to unruptured aneurysms.

Despite similar characteristic on angiography, where only the lumen of the aneurysm is assessed, ruptured and unruptured aneurysms have different characteristics. Several studies focusing on the morphology of the aneurysm wall found that the wall of ruptured aneurysms is fragile compared to that of unruptured aneurysms [18,19]. Histological analysis has shown that unruptured aneurysms are more likely to have thick intima-like walls, unlike ruptured aneurysms which are more likely to have thin degenerate walls with hyaline deposits [19]. Frosen et al. postulate that the inflammatory response with infiltration of macrophages and T-cells as well as smooth muscle cell proliferation may have been present prior to rupture leading to wall instability [18]. Wall instability leads to increased intra-aneurysmal pulsatile pressure as demonstrated by Wardlaw et al. who showed that recently ruptured aneurysms were more pulsatile that asymptomatic ones in patients with multiple aneurysms [20,21]. The increased intra-aneurysmal pulsatile pressure will likely increase the risk of coil compaction, coil migration and ultimately coil extrusion through the aneurysm dome, hence leading to recanalization.

In our study, irrespective of neck size, aneurysms which had a relatively wide neck morphology, based on dome-to-neck ratio, had a higher risk of recanalization. This is despite balloon or stent-assisted techniques employed to achieve maximum obliteration of the aneurysm. Unlike other studies [14,22,23], the unruptured group had a slightly higher aspect ratio when compared to the ruptured group but this was not statistically significant. This is presumably due to selection bias as the aneurysms were matched to aneurysm diameter and neck size. There was a trend toward a higher aspect ratio in the recanalized group when compared to the non-recanalized group.

In our study, aneurysm diameter was a statistically significant predictor of recanalization. Bavinzski et al. found tiny open spaces between coil loops at the aneurysm neck despite complete obliteration found on angiography. This finding was more frequent with larger size aneurysms, likely secondary to delayed endothelialization [24], leading to an increased risk of recanalization. Delayed organization of thrombus and lack of endothelialisation at the neck of two giant aneurysms treated with GDC coils were found by Molyneux et al. [25].

The unruptured group had a higher percentage of patients with incomplete obliteration post treatment with the majority having a residual neck. The likely explanation for this outcome is the wide neck morphology. Despite incomplete obliteration, the majority of these went on to further thrombosis unlike the ruptured group (30.6% versus 2.1%). The initial post obliteration state was not a significant predictor for recanalization. There was however a higher percentage of patients in the recanalized group who had incomplete obliteration of the aneurysm.

The majority of patients in the unruptured group had a smooth dome (67.3%) while the ruptured group were mainly irregular (61.2%). The irregular morphology may reflect the post rupture state with daughter blebs developing at the site of rupture. The precise underlying mechanism for irregular morphology is unknown and thought to be due to a combination of intrinsic and extrinsic factors including wall stress due to intraaneurysmal hemodynamics [26-28] and the perianeurysmal environment [29].

The higher recanalization rate of 40.4% in the ruptured group is significantly higher than the recently published recanalization rate of 20.3% in the entire ruptured aneurysm cohort in the same aneurysm database [6]. This is likely due to the small subset of aneurysms matched for this study and hence contributing to selection bias. It was not possible to match our entire aneurysm population due significant differences in the number of ruptured aneurysms versus unruptured aneurysms and significant differences in aneurysm size for the aneurysms excluded from this study. The recanalization rate in this study is only meaningful as a direct comparison for a matched population.

Despite the high recanalization rate, there was no re-hemorrhage in the ruptured group. This may be due to the small study population and the re-treatment for those with significant recanalization. A good outcome (Glasgow Outcome Score of 5) was achieved in majority of the patients in both groups but the ruptured group had a higher number of patients with poor outcome, including two deaths which where both due to significant vasospasm and large infarcts. The lower than expected good outcome score for the unruptured group was due to pretreatment morbidity.

Study Limitations

Our aneurysm cohort is small and selected to match the unruptured group. There may be sampling error due to the small size of the groups. This study is a retrospective assessment of neck size, dome-to-neck ratio, aspect ratio and aneurysm morphology. Neck morphology was not matched. There was a higher percentage of aneurysms in the unruptured group with wide neck morphology. This variance in neck morphology did not reach statistical significance.

Conclusion

Large neck size, wide neck morphology, large aneurysm diameter and ruptured aneurysm are significant predictors for recanalization of coiled aneurysms. Following endovascular treatment, ruptured aneurysms had a significantly increased risk of recanalization compared to matched unruptured aneurysms. The degree of recanalization of ruptured aneurysms is more significant and a higher percentage require retreatment. It takes a significantly shorter time for recanalization to occur in ruptured aneurysms compared to unruptured aneurysms. After endovascular treatment earlier, more frequent imaging follow-up is required for ruptured aneurysms compared to unruptured aneurysms.

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